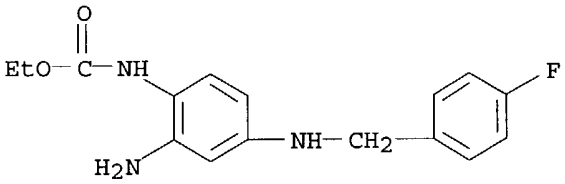
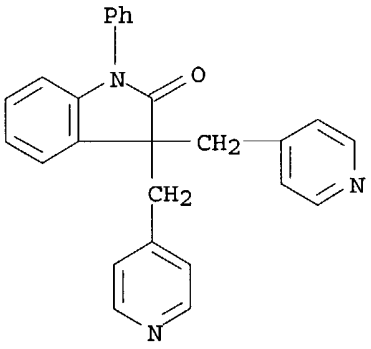
L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 150812-12-7 REGISTRY
CN Carbamic acid, [2-amino-4-[[(4-fluorophenyl)methyl]amino]phenyl]-, ethyl ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN D 23129
CN Ethyl [2-amino-4-[[(4-fluorophenyl)methyl]amino]phenyl]carbamate
CN **Retigabine**
FS 3D CONCORD
MF C16 H18 F N3 O2
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMLIST, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

57 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
59 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN
RN 105431-72-9 REGISTRY
CN 2H-Indol-2-one, 1,3-dihydro-1-phenyl-3,3-bis(4-pyridinylmethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN DuP 996
CN **Linopirdine**
FS 3D CONCORD
MF C26 H21 N3 O
CI COM
SR CAS Client Services
LC STN Files: ADISINSIGHT, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CIN, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, PHAR, PROMT, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

88 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
88 REFERENCES IN FILE CAPLUS (1907 TO DATE)

FUNCTIONAL BOWEL DISEASE / CONSTIPA

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Functional Bowel Disorders

Definition

A **functional bowel** disorder is a **functional** gastrointestinal disorder wit attributable to the mid or lower gastrointestinal tract. The **functional bow** include irritable **bowel** syndrome (IBS), **functional** abdominal bloating, f constipation, **functional** diarrhea and unspecified **functional bowel** diso female to male ratio of IBS ranges from 1:1 to 2:1 in the community, exc where there is a male predominance. The prevalence of IBS is lower in t **functional bowel** diseases can be diagnosed based on established crite exclusion of organic causes. The Rome II diagnostic criteria pertaining to framework to understand, categorize and treat these gastrointestinal disc Rome criteria have also helped to standardize the selection of patients fc and surveys. They have also allowed patient groups to be selected base predominant IBS symptom pattern (constipation, diarrhea or bloating), th to evaluate the predicted effect of a particular treatment.(1)

Diagnosis

The Rome II diagnostic criteria for IBS include at least 12 weeks or more not be consecutive, in the preceding 12 months of abdominal discomfort

has two out of three features: (1) Relieved with defecation and /or (2) On with a change in frequency of stool; and/or (3) Onset associated with a cl (appearance) of stool. Supportive symptoms of IBS include (a greater tha occurrence of) (I) Fewer than three **bowel** movements per week (II) More **bowel** movements per day (III) Hard or lumpy stools (IV) Loose (mushy) stools (V) Straining during a **bowel** movement (VI) Urgency (VII) Feeling **bowel** movement (VIII) Passing mucous during a **bowel** movement (IX) , fullness, bloating or swelling. (1)

Diarrhea-predominant IBS is associated with one or more of the supporti II, IV or VI; or two or more of II, IV or VI and none of I or V. *Constipation-* IBS is associated with one or more of the supportive symptoms I, III or V IV or VI.(1) If diarrhea or constipation are not dominant then the IBS is pr associated with abdominal discomfort or *pain*.(1)

Evaluation

A limited screen for organic **disease** is indicated to compliment a positive IBS based on the Rome II criteria. Screening should include hematology, erythrocyte sedimentation rate, stool examination for occult blood, stool f parasites and gram stain, flexible sigmoidoscopy with biopsy in those wit a flexible sigmoidoscopy and air contrast barium enema or colonoscopy i 40 with a family history of colon polyps or cancer.(2) A high erythrocyte s rate, anemia and rectal bleeding are negative predictive factors for the **fu bowel** diseases and should alert the clinician to an alternate **disease** pro needs to be evaluated further.

Intractability in *constipation predominant IBS* can be further investigated transit study, anorectal manometry, balloon expulsion test and dynamic p *Diarrhea-predominant IBS* can be further evaluated with a lactulose H2 b stool osmolarity and electrolytes, jejunal aspirate for ova and parasites a and colon transit. *Pain-predominant IBS* can be further evaluated with ab and a small **bowel** series, lactulose H2 breath test and gastrointestinal m

Treatment

Diarrhea-predominant IBS can be treated with dietary restriction (lactulos sorbitol), loperamide or diphenoxylate as well as cholestyramine. Tricycli antidepressants significantly relieve diarrhea and associated pain at leas the anticholinergic effect. Calcium channel blockers may be used as sec treatment. 5HT3 (alosetron) and 5HT4 receptor antagonists may also be controlling diarrhea-predominant IBS.(2)

Patients with *pain-predominant IBS* may benefit from treatment with antis with or without anxiolytics and avoidance of gas forming foods. Smooth m relaxants such as mebeverine, octylonium and cimetropium are worthy o trial in view of a mean response of pain in a meta-analysis of 68% compa placebo.(2) New treatment modalities in clinical trial evaluation include th agonist fedotozine.(1,2)

Constipation-predominant IBS has been shown to improve significantly w

agents in clinical trials. Osmotic laxatives like milk of magnesia or lactulo softeners may be added to the regimen if bulk agents alone are not suffic antidepressants may cause or aggravate constipation through the antich and should, therefore, be avoided in the subgroup with pain and constipa IBS.(2) Currently, phase III clinical trials are evaluating the effec tiveness receptor agonists for treatment of chronic constipation, including constipa predominant IBS.

Other potential therapies for IBS include selective serotonin re-uptake inh muscarinic agents, alpha-2 adrenergic agents, somatostatin analogs and antagonists.(2). The somatostatin analog Octreotide reduces orocecal tra increases colonic visceral sensory threshold in IBS, but has limited clinic in view of its parenteral mode of administration.(1)

Constipation

Definition

Constipation is a symptom of many diseases and is a collective term use stools are either too hard, too infrequent or to difficult to pass. Constipati defined by the presence of two or more of the following symptoms over g three months when the patient is not taking laxatives: (a) straining at defe of the time, (b) lumpy and/or hard stools > 25% of the times, (c) sensatio evacuation >25% of the time and (d) two or fewer **bowel** movements per

Historical Perspective

In the early part of the 20th century, Sir William Arbuthnot Lane advocate and ileorectal anastomosis for the treatment of a variety of disorders, incl condition referred then as chronic intestinal stasis or Arbuthnot Lanes' **di** majority of colectomies performed by Lane were for chronic constipation. 93 patients treated for constipation by colectomy or bypass. Only eight o were men and two-thirds of the women were aged 35 or under.(5)

Etiology

It is difficult to determine the underlying etiology of constipation in Lanes' However, no evidence of megacolon was present in any of the 85 women constipation. It is likely, therefore, that many of the women operated on b normal sized colon and that they were suffering from idiopathic slow-tran constipation. Associations between constipation and disorders such as p circulation, breast **disease**, infertility, estrogen deficiency and ovarian cy described.(4,5) Other studies have associated chronic constipation with t of laxatives. (5) Although slow-transit constipation without megarectum a almost exclusively, slow-transit constipation with megarectum affects ma females in equal proportion.(6-8) Table 1 summarizes the most common constipation.

Table 1 Causes of Constipation

Endocrine	insulin-dependent diabetes mellitus, hypopituita

	hypothyroidism, hypercalcemia, pseudo-hypopa pheochromocytoma, glucagonoma, pregnancy, steroid hormones in luteal and follicular phases cycle
Metabolic disorders	porphyria, uremia, hypokalemia, amyloid neuro
Neurologic disorders	Parkinson's **disease**, cerebral tumors, cerebrov accidents, multiple sclerosis, scleroderma, men aganglionosis, Chagas **disease**, hyperganglion autonomic neuropathy, spinal cord injury, major anxiety, obsessional personality disorders
Surgery resulting in localized damage to autonomic nervous plexus	pelvic surgery (cystectomy, rectopexy, hysterec
Pharmacologic agents	Opioids, anticholinergics, anticonvulsants, anta and aluminum containing), anti-Parkinsonian ag antihypertensive agents, chronic stimulant laxat (senna, cascara, anthraquinones, bisacodyl), m oxidase inhibitors, tricyclics, phenothiazines, alk (vincristine), heavy metal poisoning (lead, merc phosphorus, iron, oral contraceptives, muscle re
Obstructive **bowel** diseases	Endometriosis, carcinoma, volvulus, hernia, ber pseudo-obstruction, polyps, adhesions
Functional	Irritable **bowel** syndrome, anismus, sedentary-l patients
Dietary	Inadequate fiber or fluid intake
Primary or idiopathic	No specific underlying condition identified

Diagnostic Modalities

Preliminary evaluation of constipated patients starts with a thorough histo physical exam in order to identify changes in lifestyle, medication regime status. Patients undergoing workup of constipation should have a *flexible* sigmoidoscopy and *barium enema* for heme-negative stools or a *colonos* positive stools. Such studies enable exclusion of malignancy and other a abnormalities of the lower gastrointestinal tract. Laboratory bloodwork sh thyroid function tests, ionized calcium and glucose in order to evaluate fo hypothyroidism, hypercalcemia and diabetes. Constipation refractory to c lifestyle modifications benefits from manometric documentation of the *an inhibitory reflex* (RAIR). RAIR allows differentiation between idiopathic cc aganglionosis in whom the reflex is absent. *Anorectal manometry* also al documentation of anal sphincter pressures to rule out hypertonia and ass obstruction. *Dynamic proctography* provides cineradiographic evidence c pathology, such as rectoceles, enteroceles and rectal prolapse, that may for outlet obstruction and difficulty with **bowel** movements. *Intestinal tran* allow objective measurement of constipation. Colon transit analysis enab determination of segmental and total colon transits and thereby identifies normal and slow colonic transit.

Anatomy and Physiology

The cause of slow whole gut transit in patients with a normal-sized colon rectoanal inhibitory reflex is not completely understood. Constipation syn also be associated with a disorder of the striated muscle of the pelvic floc contracts inappropriately with attempted defecation (anismus or paradoxi puborectalis) rather than relax as in normal individuals.(8) The epidemiol constipation study in the United States noted an overall prevalence of co 14.7%. Prevalence according to subtype was 4.6% for **functional**, 2.1% for outlet and 3.4% for IBS-outlet associated constipation.(9)

Studies of colonic motility have shown that patients with slow transit cons have colonic hypersegmentation and that many have little spontaneous c or response to topical stimulation with bisacodyl.(10) This latter finding su possible abnormality of the myenteric plexus. Peptide containing nerves appear to be normal, but there may be abnormalities in the morphology c plexus.(11)

Failure of normal gastrin, motilin and pancreatic polypeptide release has documented in patients with severe constipation, although this may repre secondary phenomenon.(12,13) Measurement of sex hormones have sh abnormalities, such as hyperprolactinemia which may be related to amer other reproductive symptoms common in these patients.(14) In addition, coworkers in 1991 noted a constant reduction in estradiol, cortisol and te the luteal and follicular phases as well as reduced progesterone and , 17 hydroxyprogesterone, androstenedione and dehydroepiandrosterone in t phase of women with severe chronic constipation.(15)

Treatment

In most cases, constipation can be treated with dietary manipulation, sim enemas. However, there is a group of patients for whom medical manag unsatisfactory and in whom stimulant laxatives quickly loose their effect a myenteric plexus damage.

One approach to the therapy of chronic constipation consists of stimulati physiological as possible, intestinal motility (*Table 2*). In the colon, high a propagated contractions occur a few times a day, especially right after av after meals. These so called mass movements or giant migrating contrac provide the main propulsive force to fast colonic propulsion and often are urge to defecate. In idiopathic chronic constipation, the number and dura GMC's is smaller than in healthy subjects (16).

A new chemical class (*benzofurans*) has been shown to specifically indu to stimulate proximal colonic motility in humans. These agents also stimu pyloro-duodenal motility and accelerate delayed gastric emptying in the c The effect is mediated by selective stimulation of serotonin 5HT4 recepto facilitate cholinergic as well as non-cholinergic excitatory neurotransmiss the enterokinetic effect. This class of agents is currently being studied in clinical trials for treatment of chronic constipation.(17)

Surgical treatment is undertaken in patients with chronic idiopathic consti great reluctance and only because patients are greatly disabled in view c medical management. The severity of constipation in these individuals th colectomy is unusual. Local sphincter surgery or segmental colon resecti benefit patients with slow transit constipation. Internal sphincterotomy ma select group of individuals with hypertonic anal sphincter and impaired ou not alleviate symptoms from paradoxical puborectalis activity. Sigmoid co be performed for recurrent sigmoid volvulus. *However, total abdominal co ileorectal anastomosis* gives the best chance of a good **functional** result with severe slow transit constipation refractory to medical management (Following total abdominal colectomy with ileorectal anastomosis the life c be transformed from an existence dominated by the absence of normal b abdominal discomfort and the use of laxatives, to normality in approxima Most patients report a return of the urge to defecate after colectomy.(3,1 selection of surgical intervention for constipation depends on careful ider treatment of slow colonic transit and/or any associated pelvic floor pathol enteroceles, rectoceles and prolapse. Surgical management of carefully patients with slow transit constipation and concomitant pelvic floor hernia shown to yield satisfactory results in 89%.(19)

Although serious immediate postoperative complications are rare followir colectomy with ileorectal anastomosis, prolonged ileus tends to be a prol addition, a high incidence of small **bowel** obstruction has been noted foll colectomy for constipation. Diarrhea and fecal incontinence may also cau following total colectomy.(5)

Table 2 Treatment Options for Chronic Idiopathic Constip

Underlying pathology	Correct causative underlying conditions and elimi medications if possible
Activity level	Increase mobility
Dietary manipulations	High fiber intake (20-30 g / day) Konsyl(r) / Metar Citrucel(r) 1 tbs.PO BID Increase non-caffeinated (8-10 8 oz glasses / day)
Stool softeners	Sodium docusate 100 mg PO BID Mineral oil 1 oz PO BID
Stimulant laxatives	Pericolace(r) 1 PO QD Dulcolax(r) 5-15 mg PO if no BM for 3 or more co days
Prokinetic agents	Benzofuran PO QD (clinical trial)
Enemas	Fleets(r) enema if no BM for 3 days
Osmotic agents	Milk of Magnesia 30-60 PO QD Lactulose 30 ml PO QD-BID Polyethyleneglycol (PEG) 10-20 oz PO QD Miralax(r) 17 gm PO QD
Psychological support and evaluation as	Counseling, MMPI

indicated	
Surgical intervention	Subtotal colectomy with ileorectal anastomosis Subtotal colectomy with ileostomy Diverting ileostomy

Conclusion

Functional bowel diseases can be diagnosed based on the Rome II crit allow subgrouping of IBS into predominantly diarrhea, constipation or pai stratification of IBS based on symptomatology also facilitates establishm modalities for specific IBS types. Idiopathic slow transit constipation repr complex disorder. For the patients who develop severe and disabling idic constipation, unresponsive to dietary modification or drugs, colectomy ar anastomosis can offer great benefit. Careful physiologic and anatomic ev refractory idiopathic constipation and any associated pelvic outlet pathol to taper the surgical operation to meet the needs of the patient.

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